Please add the following new claim.

39. (New) A method for determining binding of a ligand to one or more receptors, comprising contacting a collective ligand variant population with said one or more receptors and detecting binding of said one or more receptors to said collective ligand variant population wherein said collective ligand variants are attached to peptide tags.

REMARKS

Claims 1-38 are pending in the application and claims 10-18 are under examination in the application. Claims 10, 11, 13, 14, 17, and 18 have been amended and new claim 39 has been added. Support for the amendments and new claim can be found throughout the specification and claims as filed. In particular, support for the amendment to claims 10, 11, 13, 14, 17, and 18 can be found, for example, in the original claims and on page 9, lines 26-28. Support for new claim 39 can be found, for example, on page 28, lines 28-33, and in Example I on page 38, lines 18-33. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Applicants have set forth above the amendments to the specification and claims in clean form as required under 37 C.F.R. § 1.121 (c)(i). Applicants also attach Appendix A with the marked amendments to the specification and claims indicated with brackets and underlining as required under 37 C.F.R. § 1.121 (c)(ii)

Applicants appreciate the time and helpful discussion with Applicants' representative and Examiner Garcia in the telephone conference on November 17, 2000.

The present invention provides a method for determining optimal binding of ligands to receptors. The method consists of contacting a collective ligand variant population with receptors and detecting binding of the receptors to the collective ligand variant population. The collective ligand variant population contains ligands structurally related to a parent or target ligand. The collective ligand variant population can be further divided into two or more sub-populations which can be contacted with more receptors and binding detected. In addition, the steps of dividing, contacting and detecting can be repeated one or more times. Applicants have reviewed the Office Action and respectfully traverse all grounds for rejecting the claims for the reasons that follow.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 10-18 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. The Examiner alleges that phases such as "collective ligand variant population," "binding activity," and "optimal binding activity" are defined very broadly.

Applicants submit that the specification provides sufficient description and guidance to convey to one skilled in the art the meaning of the terms recited in the claims. The specification teaches that "collective" refers to an aggregate of members that form the population or sub-population (page 10, lines 19-22). The term "ligand" is defined on page 8, lines 7-8, to be a molecule that can selectively bind to a receptor. A ligand is further described as being, for example, a polypeptide, nucleic acid, carbohydrate, lipid, or any organic derived compound including derivatives, analogues and mimetic compounds (page 8, lines 11-16). Ligands are further described as natural or synthetic organic compounds as well as recombinantly or synthetically produced polypeptides (page 8, lines 21-23). A specific example of ligands is shown in Example V, where three anti-idiotypic antibody ligands were generated by immunizing mice with a purified receptor antibody (page 50, lines 29-33).

The specification teaches that a "variant" when used in reference to a ligand is a molecule that shares a similar structure and function (page 8, lines 26-28). For example, variants can possess substantially the same or similar binding function as the parent molecule although variants can have detectable differences in chemical functional groups (page 8, line 31, through page 9, line 2). Variants are described as being directly modified such as by the mutation of an amino acid residue or the addition of a chemical moiety, or indirectly modified such as by the binding of a regulatory molecule or allosteric effector (page 9, lines 3-8). Additional examples of variants are also described such as an isoform or family member

that is distinct but related to the parent (page 9, lines 9-11). Receptor and ligand variants are further described in the specification as able to differ in chemical functional groups in their contact sites or differ in other chemical functional groups that contribute to the conformation and three-dimensional orientation of the chemical functional groups in the contact site (page 13, lines 14-19). A specific example of a polypeptide receptor variant is described in the specification as differing by one or more amino acids in a functional binding domain (page 9, lines 16-25). Further description of what constitutes relatedness of a variant polypeptide, including specific amino acid substitutions, is given on page 15, lines 6-24.

The specification teaches that a "population" refers to a group of two or more different molecules (page 9, line 26, through page 10, line 11). In addition, the specification provides a specific example of a population (see Example V, page 49, line 5, through page 55, line 15). Furthermore, specific guidance on how to generate a library containing a ligand variant population is given on page 14, lines 12-21. In addition, a graphical description of a ligand variant population is given in Example II on page 41, lines 12-27, and in Figure 1.

The specification teaches that "optimal binding" is a preferred binding characteristic of a ligand and receptor interaction, and can be ligand-receptor interactions of a desired affinity, avidity or specificity (page 10, lines 23-27). Exemplary optimal binding characteristics are also provided on page 10, line 32, through page 11, line 14. Accordingly,

Applicants submit that the specification provides sufficient description and guidance for the meaning of the terms recited in the claims.

The Office Action further alleges that the specification does not disclose an example of carrying out the claimed method, although the Examiner acknowledges that an example appears to describe the opposite case scenario. Although working examples are not required, Applicants submit that the working example taught in the specification (Example V) describing a method for determining binding of a receptor to one or more ligands can be applied to determining binding of a ligand to one or more receptors, as claimed. For example, the specification clearly teaches that methods and procedures for determining binding of a receptor to one or more ligands can similarly be applied to determine the binding of a ligand to one or more receptors (page 31, lines 5-8). Therefore, the methods described for receptor variants can also be similarly applied to ligand variants. Therefore, Applicants respectfully submit that the specification provides sufficient description and guidance for the claimed methods.

The Office Action also alleges that there is not adequate description nor examples of producing ligands by recombinant expression in melanophore cells as stated in claims 15 and 16 or tagging with an identifiable tag as stated in claim 17. Applicants submit that it would have been clear to one of skill in the art how to produce ligands by recombinant expression in melanophore cells using the description and guidance in the

specification. In particular, the specification teaches methods of using melanophore cells to express variant populations (page 24, line 11 through page 26, line 12; and Example I, page 37, line 12, through page 40, line 32).

In regard to tagging ligands, the specification teaches methods of tagging variants (page 28, line 28, through page 30, lines 24). Methods for detecting the tag, for example using antibodies specific for the peptides in FACS analysis, are also described on page 30, lines 8-20. The specification also teaches methods for tagging a variant by co-expression of a peptide tag on the parental expression vector (Example I on page 38, lines 18-33). Therefore, Applicants respectfully submit that the specification provides sufficient description for how to produce ligands by recombinant expression in melanophore cells and how to tag with an identifiable tag.

Applicants respectfully submit that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Therefore, Applicants respectfully request that these grounds of rejection be withdrawn.

Claims 10-18 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner alleges that the claims and nature of the invention regarding ligands and receptors are broad. Applicants respectfully submit

that the specification provides sufficient description and guidance to enable the claimed methods.

Regarding the alleged breadth of the claims, the specification teaches that a ligand is a molecule that can selectively bind to a receptor, that is, with a binding interaction that is detectable over non-specific interactions by a quantifiable assay (page 8, lines 7-11). The specification also teaches that a receptor selectively binds to a ligand (page 5, lines 28 to page 6, line 17). Furthermore, a specific working example of receptors and ligands is shown in Example V, where the BR96 antibody is designated as a parent receptor and anti-idiotypic antibodies are ligands (page 49, lines 8-9, and page 50, lines 29-33). Thus, based on the teachings in the specification, one skilled in the art would have readily understood that the claimed receptors and ligands are binding partners having specific binding activity.

Regarding the alleged unpredictability in the art, Applicants respectfully submit that the specification provides sufficient description and guidance to enable the invention as claimed. The Office Action acknowledges that ligand-receptor binding pairs were well known at the time of the invention. In addition, the specification teaches that ligands and receptors are specific binding molecules for each other. The specification also teaches methods for detecting binding of ligands and receptors (page 24, line 11, to page 26, line 24; and Example V, pages 49-55). Regarding variants, the specification teaches a variant shares a similar structure and function with a parent

receptor or ligand as well as methods for making variants (page 8, line 26 to page 9, line 25; page 14, lines 12-21; page 15, lines 1-24; page 19, line 29 to page 23, line 28; and Example II, pages 41-43).

Regarding the use of melanophore cells, the specification teaches methods of using melanophore cells to express variants (page 24, line 11 to page 25, line 32; Example I, pages 37-40). Furthermore, the Office Action acknowledges that it was known in the art how to make receptors using melanophore cells. Regarding making ligands, Applicants contend that one of ordinary skill in the art would have known, based on the description in the specification related to expressing receptors in melanophore cells, how to use the same procedure to express a ligand in a melanophore cell. For example, the procedures for generating DNA constructs were well known in the art, and the specific procedures for efficient transfection of DNA constructs into melanophore cells were known in the art and described in the specification (page 24, lines 12-13, and page 39, lines 1-5).

Regarding the alleged unpredictability of adding tags to ligands, the specification teaches methods for tagging with an identifiable tag (page 28, line 18 to page 30, line 24; and Example I, page 38, lines 18-33). The Office Action cites an article by Janda (Proc. Natl. Acad. Sci. USA 91:10779-10785 (1994)). However, the cited article by Janda states that a particular tagging method, phage technology, has been demonstrated by several groups (page 10782, third column, second

paragraph). Furthermore, this article is a review article and lists several references that have successfully used different tagging methods. Thus, Janda supports the teachings in the specification that tagging a ligand variant would have been predictable.

The Office Action again alleges that no working examples of the claimed methods are provided. As discussed above, a working example is not required, however, a working example in the specification, Example V describing receptor variants, is applicable to ligand variants. Furthermore, guidance in the specification on page 31, lines 5-8, as discussed above, explicitly states that methods and procedures for determining binding of a receptor to one or more ligands can similarly be applied to determine the binding of a ligand to one or more receptors.

Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 17 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for use of the word "identifiable" in reference to a tag.

Applicants submit that the specification provides sufficient description and guidance for the meaning of the term "identifiable" in that one of skill in the art would understand that the tag allows identification of the ligand variant. This meaning is supported in the specification, for example, on page 28, lines 30-33, and page 30, lines 5-24. However, solely in order to further prosecution, the term "identifiable" has been deleted from claim 17. Accordingly, the rejection has been rendered moot, and it is respectfully requested that the rejection be removed.

Rejections under 35 U.S.C. § 102

Claims 10-14, 17 and 18 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Combs et al. (J. Am. Chem. Soc. 118:287-288 (1996)). The Examiner alleges that Combs et al. discloses a method for using a library of ligands that direct non-peptide binding elements into the specificity pocket of an SH3 protein and that the library was tagged and decoded to find an optimal binding ligand.

Applicants respectfully submit that the claims are novel over the Combs et al. reference. The claims, as amended, are directed to methods for determining binding of a ligand to two or more receptors by contacting a collective ligand variant population with two or more receptors and detecting binding of the two or more receptors to the collective ligand variant population. Combs et al. does not teach contacting a collective ligand variant population with two or more receptors.

Furthermore, Combs et al. does not teach detection of binding of two or more receptors to a ligand population. Thus, the Combs et al. reference does not teach the method of the claimed invention and, therefore, it cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 10-14 and 18 also stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Wilson-Lingardo et al. (J. Med. Chem. 39:2720-2726(1996)). The Examiner alleges that Wilson-Lingardo et al. describes pooling strategies for combinatorial libraries as well as iteratiave deconvolution in which the libraries are broken down into smaller subsets.

Applicants respectfully submit that the claims are novel over the Wilson-Lingardo et al. reference. The claims, as amended, are directed to methods for determining binding of a ligand to two or more receptors comprising contacting a collective ligand variant population with two or more receptors by detecting binding of the two or more receptors to the collective ligand variant population. Wilson-Lingardo et al. does not teach contacting a collective ligand variant population with two or more receptors. Furthermore, Wilson-Lingardo et al. does not teach detection of binding of two or more receptors to a ligand population. Thus, the Wilson-Lingardo et al. reference does not teach the method of the claimed invention and, therefore, it cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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